REMARKS

This is intended as a full and complete response to the Final Office Action dated July 29, 2008. Please consider the claims pending in the application for the reasons discussed below.

Claims 1-12 and 17-29 remain pending in the application and are shown above. Claims 1-12 and 17-29 stand rejected by the Examiner. Claims 1, 18, and 24 have been amended to clarify the claimed subject matter. Support for the amended claims can be found on page 7, lines 9-16, and page 9, lines 20 to page 10, lines 1-6, as well as page 10, lines 23-38. Applicants assert that no new matter has been added and respectfully request entry of the claims as amended.

Rejections under 35 U.S.C. § 103

Claims 1-3, 5-11, 17-20, 22-24, 27 and 29 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over *Parikh et al.* (US 2002/0106403, hereinafter "*Parikh*") in view of *Caruso et al.* (EP 1116516, hereinafter "*Caruso*"). Applicants have amended claims 1, 18, and 24 to clarify the claimed subject matter and respectfully traverse the rejection.

To establish prima facie obviousness of a claimed invention, all of the claim limitations must be taught or suggested by the prior art. (*See* MPEP 2143.03).

Parikh teaches dispersing surface stabilized microparticles (drug particles) throughout a bulking matrix which dissolves in a rapid disintegration time upon contact with an aqueous environment, thereby rapidly releasing the stabilized microparticles without having particle agglomeration phenomenon.

Parikh does not teach or suggest capsules having a core and a shell structure. Particularly, *Parikh* does not teach, suggest, or otherwise render obvious "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, the shell comprising a high permeability to release the slightly soluble active ingredient within 60 minutes," as recited in amended claim 1.

The surface modifier (alleged to be the "shell" by the Examiner) is not equivalent to Applicants' shell because *Parikh* does not teach that the surface modifier is stable and water-insoluble compound presented within the microparticles can be diffused through the layer of the surface modifier. Rather, *Parikh*'s surface modifier is **adsorbed** on to the surface of micronized particles and is dissolved together with the microparticles, which implies a non-stable capsule shell. (See *Parikh*, paragraph [0010])

Since the adsorbed surface modifier dissolves during dissolution of the primary particle it does not provide a diffusion barrier and does not control the release of the compound from the primary particle. Paragraph [0025] of Parikh particularly refers to this point by stating:

> "*The rate of **dissolution** or release of the active ingredient may also be affected by the nature of the medicament and the **microparticle composition** such that it may be rapid (5-60 sec) or intermediate (on the order of 75% disintegration in 15 minutes) or sustained-released.*" (Emphasis added)

Hence, Parikh does not disclose that the compound diffuses through a shell but merely dissolves. Furthermore, the particle composition and not the surface modifier controls the release rate.

In fact, the surface modifier forms a diffusion barrier for the water insoluble compound. From a thermodynamic point of view, it is energetically unfavourable for the compound to diffuse through the layer of adsorbed surface modifier into an aqueous environment. The hydrophobic water-insoluble compound is shielded from the aqueous environment by the surface modifier which is energetically favoured. Hence, no diffusion through the layer of surface modifier occurs and the surface modifier acts as diffusion barrier. This also becomes evident from the point that the surface modifier **stabilizes** the primary particle in the suspension prior to forming the dosage. Would the surface modifier allows diffusion, the primary particles would dissolve in the suspension and no dosage with primary particles could be formed. This clearly shows that no

diffusion occurs through the layer of adsorbed surface modifier in an aqueous environment.

The inference that the adsorbed surface modifier is dissolved during dissolution of the microparticles is further supported by *Parikh*'s own argument made during their prosecution with USPTO. In response to prior art rejection, *Parikh* describes "*the soluble drug is first mixed with surface stabilizing agents to form an aqueous suspension that is subjected to particle fragmentation to form a homogeneous aqueous suspension. Thereafter, the homogeneous suspension is admixed with a matrix prior to drying to form drug-containing particles that rapidly dissolve and release the drug component in an aqueous environment.*" (*See* US 2002-0106403, page 20, paragraph 1, 2004-12-16 Applicant Arguments/Remarks) Therefore, it becomes evident that the adsorbed surface modifier, *i.e.,* the alleged shell, is not in a stable status that allows the drug component to diffuse through during release of the drug component, but rather rapidly **dissolved** together with the drug component in an aqueous environment as described in *Parikh*'s disclosure.

In the Advisory Action, the Examiner asserts that the shell is dissolved and therefore becomes more permeable, by citing a dictionary showing the meaning of the word "permeable" refers to "capable of being permeated," and the word "permeate" refers to diffuse through or penetrate something, upon which the Examiner concluded that the penetration occurs as the shell dissolves. Applicants respectfully disagree since there is no direct connection between penetration and dissolution. According to *Merriam Webster Online Dictionary*, the term "dissolve" is defined as to become dissipated or decomposed, or to become fluid, whereas the term "penetrate" is defined as to pass, extend, pierce, or diffuse into or through something. (*See* **http://www.merriam-webster.com/dictionary/dissolve**, and **http://www.merriam-webster.com/dictionary/penetrate**, accessed November 30, 2008) An object that is dissolvable does not necessarily has to be penetrated. Instead, penetration requires something sustained in a certain form in order for an object to pass, extend, or diffuse through. As *Parikh* describes the surface stabilized drug-containing particles to be dissolved rapidly, it is reasonable to interpret the surface modifier is not stable during

release of drug component, but rather dissipated, decomposed or become fluid in order to release the drug component in an aqueous environment. Therefore, the surface modifier taught by *Parikh* does not correspond to Applicants' shell which is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, as recited in amended claim 1.

Caruso does not cure the deficiencies of *Parikh*. *Caruso* discloses a controlled release of the encapsulated material by releasing **a small amount** of active substance constantly over a long time period with a **high diffusion barrier** across the wall of the capsule. (*See* paragraph [0012], lines 29-34) (Emphasis added)

Caruso does not specifically mention the capsule shell has high permeability for the active substance as claimed in Applicants' claim 1. Although *Caruso* discloses that the permeability and porosity of the capsule can be controlled by the selection of the polyelectrolyte used for the capsule shell and the number of polyelectrolyte layers used, thicker shells, reduced pore sizes and porosity of the shells, and smoother outer surface are characteristics suggested and desirable in terms of *Caruso*'s capsules. (*See* page 4, lines 5-9) Particularly, paragraph [0055] includes the following statement:

> "*Capsules produced when the microcrystals were dispered with surfactant (either positively or negatively charged) exhibit a much smoother texture and lower porosity than those produced from PSS-dispersed microcrystals...In contrast, it was* ***difficult to discern pores*** *in the very smooth textured polymer capsules when surfactant was used to disperse the microcrystals, suggesting an average pore size of less than about 5-10 nm.*" (Emphasis added)

Amphiphilic substance is used in *Caruso*'s capsules to control the porosity. In view of paragraph [0038] stating that the type of amphiphile determines the porosity and hence the permeability, it is evident that small molecular surfactants, for example, phospholipids as used by *Caruso* and *Parikh*, form very small pores and hence reduce the permeability of the polyelectrolyte layer, so that it is possible to achieve a controlled release of the encapsulated material by releasing **a small amount** of active substance

constantly over a long time period with a **high diffusion barrier** across the wall of the capsule, as described in *Caruso's* disclosure.

Furthermore, in connection with release time for forming hollow capsules, paragraph [0053] of *Caruso* states that "*the release rate could be altered by varying the* ***ratio of ethanol to water*** *in the dissolving medium*" (Emphasis added). Hence, according to paragraph [0053] the release rate is determined by the nature of the **external** solute. For pharmaceutical applications, the physiological environment cannot be changed so that it is irrelevant that the nature of the external solute determines the release rate. Moreover, the release rate in *Caruso* is significantly reduced when the amount of ethanol is reduced, as shown in paragraph [0053] of *Caruso*. For example, the release rate is about 100 times smaller when only a 5 vol% aqueous ethanol solution is used. Consequently, if no ethanol is used to have a physiologic environment, the release time would even be longer. These findings correspond to the general statement in *Caruso*, see paragraphs [0012] and [0038] discussed above, that the capsules are suitable for **sustained** release.

In view of the foregoing, a skilled person, when considering *Caruso*, would consider *Caruso* as a sustained release system using a high diffusion barrier across the wall of the capsule for the release of a small amount of active substance and thus would not be motivated to modify *Parikh* to yield "fast-releasing capsules having a high permeability for the slightly soluble active ingredient," and "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, and the shell comprising a high permeability to release the slightly soluble active ingredient within 60 minutes," as recited in amended claim 1. As *Parikh* and *Caruso*, alone or in combination, fail to render obvious amended claim 1, withdrawal of the rejection to claim 1 and claims dependent thereon is respectfully requested.

Similarly, claims 18 and 24 have been amended to include the limitation "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient." In view of the

reasons stated above, claims 18 and 24 as amended should be patentably distinct over *Parikh* and *Caruso*. Withdrawal of the rejection to claims 18 and 24 and claims dependent thereon is therefore respectfully requested.

Claims 4, 25 and 28 are rejected in previous office under 35 U.S.C. 103(a) as allegedly being unpatentable over *Parikh* and *Caruso* as applied above, and further in view of *Green et al.* (US 2001/0055611). Applicants respectfully traverse the rejection.

Parikh and *Caruso* are discussed above. *Green* is concerned with delaying the release of the drug for a time at least sufficient to mask the taste in the mouth before swallowing, and typically for a longer period of time to provide controlled or sustained release of the drug after swallowing by a fast dispersing freeze-dried dosage form containing drug particles which may be uncoated or coated with a polymer or lipid material." (See paragraph [0010]) *Green* also discloses a carrier material including gelatin and mannitol in a ratio of 1:0.13 to 1:1.2. (Examples 1–5)

Green does not cure the deficiencies of *Parikh* and *Caruso* as discussed herein with respect to the independent claims from which claims 4, 25, and 28 depend. *Green* does not mention the use of microcapsules having core-shell structures, not does it teach or suggest the active material to be encompassed by a material with high permeability. Specifically, *Green* does not teach, suggest, or otherwise render obvious "fast-releasing capsules having a high permeability for the slightly soluble active ingredient," and "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient, the shell comprising a high permeability to release the slightly soluble active ingredient within 60 minutes," as recited in amended claim 1. Rather, *Green* teaches a controlled or sustained release of the drug for a longer period of time.

In fact, *Green* teaches away from *Parikh* by employing and striving to attain **larger sized particles**. As disclosed in col. 5, lines 9-14, *Green* states "*the larger sized particles employed allows for the formation of a continuous intact coating on the drug particles which prevents or minimizes early release of the drug during processing.*" *Green* further teaches that the optimum coated particle size is in a region of about 50

µm to 400 µm, preferably about 100-300 µm (*Id.*), which is contradicted to *Parikh* that teaches using particle size measured between 0.05µm to 10µm, preferably between 0.2 µm to 5 µm. Therefore, one of ordinary skill in the art, when considering *Green*'s disclosure, would not be motivated to modify or combine *Green* with *Parikh* to arrive at Applicants' invention defined in claim 1. Since claim 4, 25 and 28 depends from claim 1 and contains all the limitations of claim 1, Applicants respectfully assert that claim 4, 25 and 28 should be allowable at least for the same reasons stated above. Withdrawal of the rejection to claim 4, 25 and 28 is respectfully requested.

Claims 12 and 21 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over *Parikh* in view of *Caruso* and further in view of *Virgalitto et al* (US 2005/0089548). Applicants respectfully traverse the rejection.

Parikh and *Caruso* are discussed above. *Virgalitto* teaches a sustained release mechanism using microcapsules (edible film) contained with an active agent. *Virgalitto* discloses the film-forming material is capable of rapidly dissolving in water or oral cavity to release the active agent contained in the film. (*See* paragraph [0024]) *Virgalitto* also discloses preparing an aqueous solution of film-forming materials, adding microcapsules comprising active agent, casting the resultant mixture onto a releasable backing media, and drying the film. (*See* Paragraph [0074])

Virgalitto fails to overcome the deficiencies of *Parikh* and *Caruso* as discussed herein with respect to the independent claims from which claim 12 depends. Although *Virgalitto* mentions the use of microcapsules containing active agents, *Virgalitto*'s film is **rapidly dissolved**, break-down and distintegrated upon contact with moisture to release the active agent. (*See* paragraph [0019]) Since *Virgalitto,* alone or in combination with *Parikh* and *Caruso,* does not teach, suggest, or otherwise render obvious "the shell is stable to allow diffusion and release of the active ingredient, while maintaining a stable aqueous suspension during release of the active ingredient," nor does it disclose the edible film (shell) having high permeability, as recited in amended claim 1, from which claim 12 depends, Applicants respectfully assert that claim 12

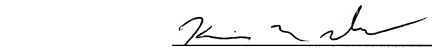
should be allowable at least for the same reasons stated above. Withdrawal of the rejection to claim 12 is respectfully requested.

Similarly, claim 21 should be allowable for the same reasons stated above as claim 21 depends on amended claim 18 and contain all the limitations of claim 18. Therefore, Applicants request withdrawal of the rejection and allowance of claim 21.

In conclusion, the references cited by the Examiner, alone or in combination, do not teach, show, or suggest the invention as claimed.

Having addressed all issues set out in the Final Office Action, Applicants respectfully submit that the claims are in condition for allowance or in better form for appeal, and respectfully requests that the claims be allowed.

Respectfully submitted,



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